Indefiniteness Rejections

The Examiner had rejected Claims 1, 3, 6-9,11, and 17-20, for indefiniteness under 35 U.S.C. § 112, second paragraph. The Applicant has amended Claims 3 and 11 to, respectively, delete the term activated and replace the term p-toluensulfonate with p-toluenesulfonic acid in view of the Examiner's rejection of these claims. Applicant respectfully traverses the remaining rejections.

The Examiner alleges Claims 1, 6-9, and 17-20, are indefinite since the phrase "sufficient to produce" is unclear as to whether the reaction must merely be initiated or completed within the specified time limits. Applicant submits the phrase "sufficient to produce" is clear on its face and modifies "oxazolidinone derivative" in the first step of Claim 1 and "N-[N-(3,3-dimethylbutyl)-L-α-aspartyl]-L-phenylalanine 1-methyl ester" in the second step of Claim 1. As to the whether the reaction has only been initiated or is completed, Applicant further submits the reaction must have been initiated; however, the claim includes all points up to and including reaction completion. The key is that at least some of the chemical compounds modified by the phrase be produced.

"In reviewing a claim for compliance with 35 U.S.C. 112, second paragraph, the examiner must consider the claim as a whole to determine whether the claim apprises one of ordinary skill in the art of its scope and, therefore, serves the notice function required by 35 U.S.C. 112, second paragraph." MPEP 2173.02, p. 2100-194, right column, *emphasis provided.* Applicant submits that one of ordinary skill in the art would, upon reading the claim, be apprised the claim recites a process to produce at least a minimal amount of the chemical compounds modified by the phrase. The same can be said of Claims

6-9 and 17-20. Accordingly, the Applicant respectfully requests reconsideration and withdrawal of this rejection.

Obvioisness Rejections

The Examiner had rejected Claims 1, 2, 4-10, 12, 14, and 16-20, under 35 U.S.C. § 103(a) as being obvious over K. Burger, et al, "Regiospecific Reactions with ω-carboxy-α-amino acids -- A Simple Synthesis of Aspartame", *Chemmiker Zeitlung*, 1990, 114(7-8), pp. 249-251 [hereinafter "Burger"] and further in view of U.S. Patent No. 5,510,508 to Claude et al [hereinafter "Claude"]. Applicants respectfully traverse the rejections.

The present invention relates to the synthesis of N-[N-(3,3-dimethylbutyl)-L-α-aspartyl]-L-phenylalanine 1-methyl ester [hereinafter, neotame] via novel oxazolidinone derivatives. Specification, page 4, lines 22 to 24. According to the present invention, neotame is synthesized by reacting N-(3,3-dimethylbutyl)-L-aspartic acid and a carbonyl compound in a solvent for a time and at a temperature sufficient to produce an oxazolidinone derivative. Specification, page 5, lines 1-10. Next, the oxazolidinone derivative is reacted with phenylalanine or phenylalanine methyl ester in a solvent for a time and at a temperature sufficient to produce neotame. Id. The solvents used in the first and second steps can be the same solvent.

The present invention provides a great advantage in the production of neotame since oxazolidinone derivatives are used as starting materials rather than aspartame which requires purification and isolation prior to use in food grade sweetener preparation.

The result is more efficient and cost-effective methods of preparing high purity neotame from readily available or readily obtainable materials. Specification, page 4, lines 15-18.

Burger teaches the synthesis of oxazolidinones from L-aspartic acid and hexafluoroacetone. Burger does not, however, disclose the synthesis of oxazolidinone derivatives from N-alkyl-L-aspartic acid and hexafluoroacetone. It can not be said that two different chemical compounds with the same root name are the same compounds. N-alkyl-L-aspartic acid may behave differently than L-aspartic acid. Also, there is no motivation in Burger to substitute N-alkyl-L aspartic acid for L-aspartic acid or to produce neotame via Burger's process. As a reference, Burger cannot stand alone to render the present invention obvious. Accordingly, Applicant respectfully requests reconsideration and withdrawal of this rejection.

Claude does not remedy the deficiencies of Burger. Claude relates to "a synthetic route which uses aspartame as the starting material." Claude, col.1, lines 33-37. Claude's method of preparing neotame "comprises treating a solution of aspartame and 3,3-dimethylbutyraldehyde, at room temperature, with hydrogen . . . in the presence of a catalyst based on platinum or palladium." Claude, col. 2, lines 1-17, *see also*, Example 1 and Claim 1. However, as stated above, the present invention utilizes oxazolidinone derivatives to produce neotame. While the Examiner is correct that aspartame and neotame appear to be structurally similar, aspartame and neotame have very different chemical, physical, and physiological properties.

Specifically, the melting point of neotame is 80°C, while that of aspartame is about 248-250°C. Additionally, neotame has much higher solubility in organic solvents than aspartame, and a much lower solubility in water. Further, neotame is more stable than

aspartame under certain pH conditions. Neotame has a higher sweetness potency than aspartame. The impurity profile for neotame is very different than that of aspartame. To wit, neotame impurities may include dialkyl aspartame, dialkyl imidazolidinone, demethylated neotame, and methylated neotame. On the other hand, aspartame impurities may include α- and β-tripeptide, demethylated α- and β-tripeptide, and β-aspartame. As can be seen, neotame has more non-polar impurities than aspartame. One of ordinary skill in the art would not predict, despite the seeming structural similarities, that chemical processes applicable to aspartame would be equally applicable to neotame.

As the Examiner is aware, the "presumption of obviousness based on a reference disclosing structurally similar compounds may be overcome where there is evidence showing there is no reasonable expectation of similar properties in structurally similar compounds. MPEP 2144.09, page 2100-149, left column (*citing*, *In re May*, 574 F.2d 1082 (CCPA 1978)). One would surmise the same logic is as applicable, if not more applicable, to the production of seemingly structurally similar chemical compounds. Since the Applicant has provided evidence that aspartame and neotame have different properties, there is not, as the Examiner states, an "exceptionally strong" expectation of success. Without an expectation of success, Claude is not a proper reference. To say the very least, Burger is incomplete for obviousness purposes and Claude does not remedy Burger's deficiencies. Accordingly, Applicant respectfully requests reconsideration and withdrawal of this rejection.

CONCLUSION

Wherefore, reconsideration of the rejected claims is respectfully requested as is the expeditious allowance of all pending claims in light of the foregoing amendments and remarks in support of patentability. If any issues remain, the Examiner is invited to call the Applicant's undersigned attorney to discuss matters further.

Applicant's undersigned attorney may be reached in our New York office by telephone at (212) 218-2100. All correspondence should continue to be directed to our below-listed address.

Respectfully submitted,

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Marked-Up Version to Show Revisions Made to the Specification

ABSTRACT

Synthesis of N-[N-(3,3-dimethylbutyl)-L-α-aspartyl]-L-phenylalanine 1-methyl ester [is produced using novel] by treating N-(3,3-dimethylbutyl)-L-aspartic acid with aldehydes or ketones to give oxazolidinone derivatives, which are condensed with L-phenylalanine methyl ester.

Paragraph on page 8, lines 1-11:

In certain embodiments of the present invention, a catalyst may be present during the reaction of N-(3,3-dimethylbutyl)-L-aspartic acid and the carbonyl compound. Suitable catalysts include, without limitation, [p-toluenesulfonate] p-toluenesulfonic acid. In certain embodiments of the present invention, an acid may be present during the reaction of N-(3,3-dimethylbutyl)-L-aspartic acid and the carbonyl compound. Suitable acids include, without limitation, formic acid, acetic acid, [p-toluene sulfonic acid] p-toluenesulfonic acid, methane sulfonic acid, 10-camphorsulfonic acid and combinations thereof.

Paragraph on page 16, lines 5-14:

Neo-aspartic acid (5 mmol) was dissolved in 2,2-dimethoxypropane (10 ml) and 1,4-dioxane (10 ml). [p-Toluene sulfonic acid] p-Toluenesulfonic acid (0.5 mmol) was added to the reaction mixture and refluxed for 48 hours. The solvent was removed from the reaction mixture, extraction using dichloromethane was performed, the organic layer was concentrated by vacuo and the residue was checked via 1H NMR. 2-[(4S)-3-(3,3-

dimethylbutyl)-2,2-dimethyl-5-oxo-1,3-oxazolan-4-yl]acetic acid was obtained in about a 20% yield and with low purity.

Marked-Up Version to Show Revisions Made to the Claims

3. (Amended) The process according to claim 1, wherein the [activated] carbonyl compound is selected from the group consisting of dimethyl or diethyl acetals of hexafluoroacetone, trichloroacetaldehyde, tribromoacetaldehyde, hexachloroacetone, formaldehyde, benzaldehyde, substituted benzaldehydes and combinations thereof.

11. (Amended) The process according to claim 10, wherein the catalyst is [p-toluenesulfonate] p-toluenesulfonic acid.

13. (Amended) The process according to claim 12, wherein the acid is selected from the group consisting of formic acid, acetic acid, [p-toluene sulfonic acid] p-toluenesulfonic acid, methane sulfonic acid and combinations thereof.